

10/634,641

FILE 'MEDLINE' ENTERED AT 09:32:01 ON 28 SEP 2004

FILE 'HCAPLUS' ENTERED AT 09:32:01 ON 28 SEP 2004

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FILE 'BIOSIS' ENTERED AT 09:32:01 ON 28 SEP 2004

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FILE 'EMBASE' ENTERED AT 09:32:01 ON 28 SEP 2004

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=> d his

(FILE 'HOME' ENTERED AT 09:30:11 ON 28 SEP 2004)

FILE 'REGISTRY' ENTERED AT 09:30:19 ON 28 SEP 2004

L1 STRUCTURE UPLOADED

L2 1 S L1 SSS SAM

L3 59 S L1 SSS FULL

AK - C(114-32)

FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE' ENTERED AT 09:32:01 ON 28 SEP 2004

=> s l3

L4 304 L3

=> s l4 and (antitumor? or anti(2a)tumor? or antitumour? or anti(2a)tumour? or cancer? or neoplas? or melanom? or leukem?)

L5 29 L4 AND (ANTITUMOR? OR ANTI(2A) TUMOR? OR ANTITUMOUR? OR ANTI(2A) TUMOUR? OR CANCER? OR NEOPLAS? OR MELANOM? OR LEUKEM?)

=> dup rem l5

PROCESSING COMPLETED FOR L5

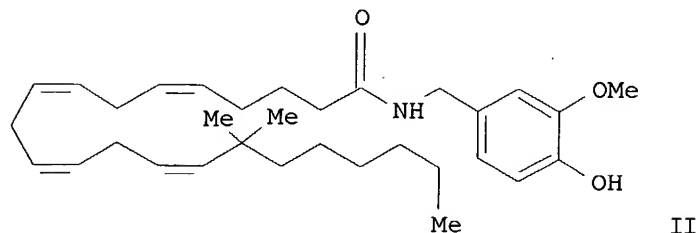
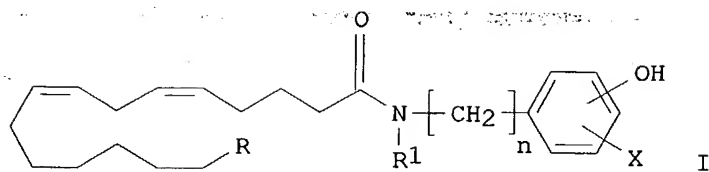
L6 17 DUP REM L5 (12 DUPLICATES REMOVED)

=> d l6 abs cbib kwic hitstr 1-17

L6 ANSWER 1 OF 17 HCAPLUS. COPYRIGHT 2004 ACS on STN

GI

DELACROIX



AB Analogs of anandamide and arvanil of formula I ($n = 0-5$, $X = H$, C1-6 alkyl, halogen, hydroxy, or C1-6 alkoxy, $R_1 = H$, C1-6 alkyl, $R =$ substituted alkyl) were prepared as analgesic agents which bind to CB1 and VR1 receptors. Thus, but-2-yn-1,4-diol was treated with K_2CO_3 , CuI, NaI and Me hex-5-ynoate to give the 1-hydroxy-deca-5,8-diynoic acid Me ester which was treated with but-3-yn-4-ol to give the corresponding trynoic acid Me ester. The trynoic ester was reduced to the trienoic acid Me ester using $Ni(OAc)_2$, ethylenediamine, and $NaBH_4$ in EtOH, and then treated with triphenylphosphine, imidazole, and I2 to give Me 14-triphenylphosphino-tetradeca-all-cis-5,8,11-trienoate iodide. This iodide was reacted with the corresponding aldehyde to give 16,16-dimethyl-docosa-5,8,11,14-all-cis-tetraenoic acid Me ester which upon conversion of the acid and reaction with 4-hydroxy-3-methoxy benzyl amine yielded II. II had an EC_{50} of 0.7 nM against the VR1 and a K_i of 261.8 nM for CB1. The analogs provide analgesic effects in vivo, and are useful in pain management. In addition, the analogs may be used as **anti**-proliferative/**anti-tumor** agents, vasodilators, and in other applications. Several of the anandamide and arvanil analogs are more potent than anandamide and arvanil.

2004:513343 Document Number 141:71387 Preparation of anandamide and arvanil analogs as potential analgesics which bind CB1 and VR1. Martin, Billy R.; Razdan, Raj K.; Di Marzo, Vincenzo (USA). U.S. Pat. Appl. Publ. US 2004122089 A1 20040624, 25 pp., Cont.-in-part of U.S. Ser. Number 170,204. (English). CODEN: USXXCO. APPLICATION: US 2003-365607 20030213. PRIORITY: US 2001-PV299199 20010620; US 2002-170204 20020613.

AB . . . analogs provide analgesic effects in vivo, and are useful in pain management. In addition, the analogs may be used as **anti**-proliferative/**anti-tumor** agents, vasodilators, and in other applications. Several of the anandamide and arvanil analogs are more potent than anandamide and arvanil.

ST anandamide arvanil analog prepn; cannabinoid vanilloid receptor binding anandamide arvanil analog; analgesic antiproliferative **antitumor** vasodilator anandamide arvanil analog

IT 94421-68-8DP, Anandamide, analogs 128007-31-8DP, Arvanil, analogs 322399-51-9P 322399-54-2P 322399-59-7P 322399-60-0P 342882-76-2P 342882-77-3P 342882-78-4P 439079-98-8P 439079-99-9P 439080-00-9P 439080-02-1P 439080-03-2P 439080-04-3P 439080-05-4P 710294-67-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)

(preparation of analogs of eicosanoid analogs of anandamide and arvanil as
analgesics, antiinflammatories, vasodilators, and antiproliferatives
which bind to CB1 or VR1 receptors)

IT 128007-31-8DP, Arvanil, analogs 322399-51-9P

322399-54-2P 322399-59-7P 322399-60-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)

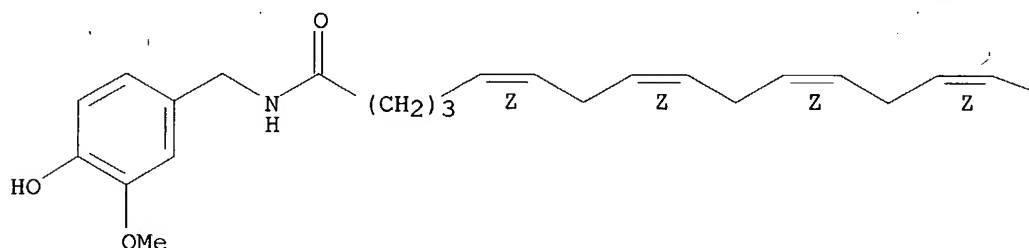
(preparation of analogs of eicosanoid analogs of anandamide and arvanil as
analgesics, antiinflammatories, vasodilators, and antiproliferatives
which bind to CB1 or VR1 receptors)

RN 128007-31-8 HCAPLUS

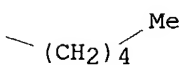
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-,
(5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

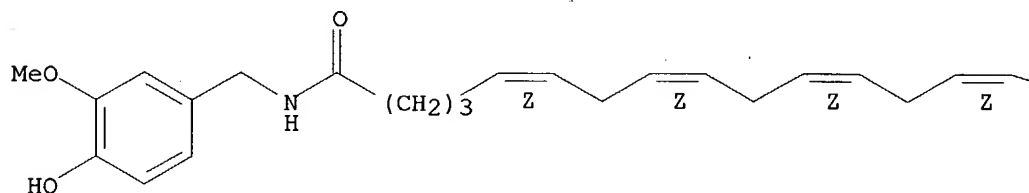


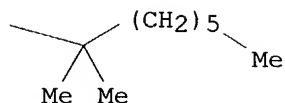
RN 322399-51-9 HCAPLUS

CN 5,8,11,14-Docosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-
dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



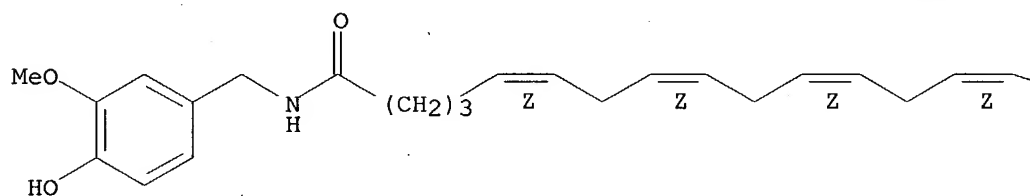


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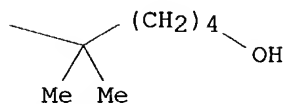
CN 5,8,11,14-Eicosatetraenamide, 20-hydroxy-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

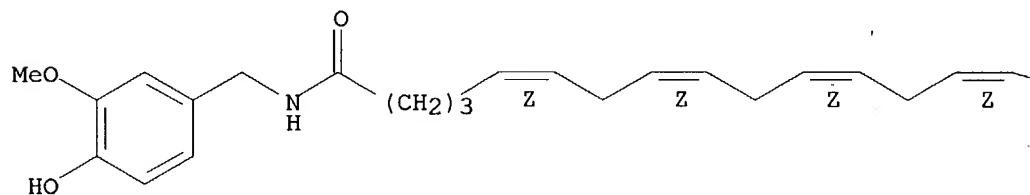


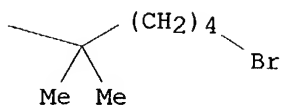
RN 322399-59-7 HCAPLUS

CN 5,8,11,14-Eicosatetraenamide, 20-bromo-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



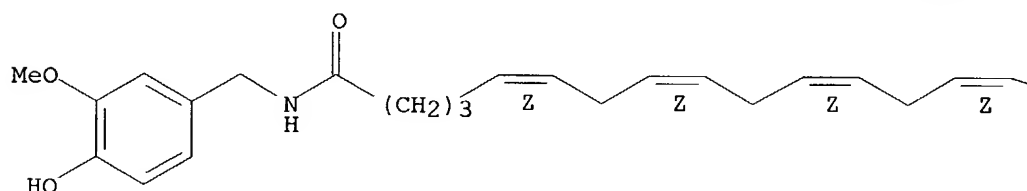


RN 322399-60-0 HCAPLUS

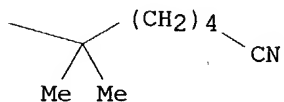
CN 5,8,11,14-Eicosatetraenamide, 20-cyano-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L6 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The present invention provides an **antitumor** pharmaceutical composition comprising a N-vanillyl fatty acid amide containing a saturated or unsatd.

fatty acid residue containing 14 to 32 carbon atoms which is related to capsaicin. An **antitumor** pharmaceutical composition comprising a N-vanillyl fatty acid amide has a low side-effect and a high **antitumor** effect, in particular against **melanoma** and **leukemia**, and has a very low pungency, a stimulatory and a preinflammatory effect. For example, the reaction of 0.2309 g of vanillylamine with 0.5919 g of 4,7,10,13,16,19-docosahexaenoic acid (C22:6, DHA) gave 0.311 g of colorless or citrine amorphous-like solid of N-vanillyl-4,7,10,13,16,19-docosahexaenamide (Dohevanyl).

Antitumor effects of Dohevanyl were compared to those of capsaicin. Compared with capsaicin, Dohevanyl was very low in the degree of hotness and stimulus, and had a higher **antitumor** effect with a low action to the normal cells. Both capsaicin and Dohevanyl induced apoptosis to cause the cell death.

2004:470289 Document Number 141:17594 **Antitumor** pharmaceutical composition comprising N-vanillyl fatty acid amide. Takahata, Kyoya

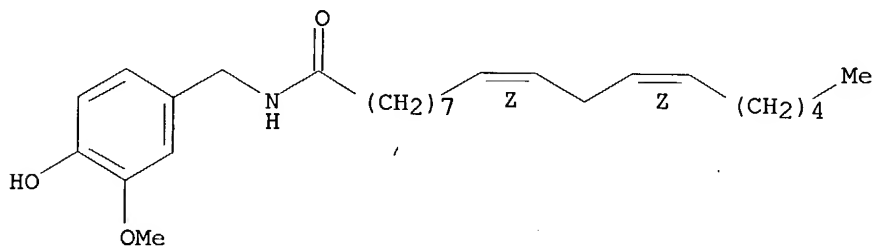
(Kureha Chemical Industry Company, Limited, Japan). Eur. Pat. Appl. EP 1426047 A1 20040609, 22 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK. (English). CODEN: EPXXDW. APPLICATION: EP 2003-254668 20030725. PRIORITY: JP 2002-353649 20021205.

- TI **Antitumor** pharmaceutical composition comprising N-vanillyl fatty acid amide
- AB The present invention provides an **antitumor** pharmaceutical composition comprising a N-vanillyl fatty acid amide containing a saturated or unsatd. fatty acid residue containing 14 to 32 carbon atoms which is related to capsaicin. An **antitumor** pharmaceutical composition comprising a N-vanillyl fatty acid amide has a low side-effect and a high **antitumor** effect, in particular against **melanoma** and **leukemia**, and has a very low pungency, a stimulatory and a preinflammatory effect. For example, the reaction of 0.2309 g of. . . vanillylamine with 0.5919 g of 4,7,10,13,16,19-docosahexaenoic acid (C22:6, DHA) gave 0.311 g of colorless or citrine amorphous-like solid of N-vanillyl-4,7,10,13,16,19-docosahexaenamide (Dohevanyl). **Antitumor** effects of Dohevanyl were compared to those of capsaicin. Compared with capsaicin, Dohevanyl was very low in the degree of hotness and stimulus, and had a higher **antitumor** effect with a low action to the normal cells. Both capsaicin and Dohevanyl induced apoptosis to cause the cell death.
- ST vanillyl fatty acid amide prepn **antitumor**
- IT Amides, biological studies
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(fatty; preparation of **antitumor** vanillyl fatty acid amides)
- IT **Antitumor** agents
Apoptosis
Human
Leukemia
Melanoma
(preparation of **antitumor** vanillyl fatty acid amides)
- IT 404-86-4, Capsaicin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(comparison with; preparation of **antitumor** vanillyl fatty acid amides)
- IT **16729-47-8P**, N-Vanillyllinoleamide **58493-49-5P**, N-Vanillylloleamide **69693-12-5P**, N-Vanillylmyristamide **104899-01-6P** **457643-60-6P**, N-Vanillylricinoleamide **571203-58-2P**, Dohevanil **698373-40-9P** **698373-42-1P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **antitumor** vanillyl fatty acid amides)
- IT 9001-62-1, Novozyme 435
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of **antitumor** vanillyl fatty acid amides)
- IT 112-62-9, Methyl oleate 112-63-0, Methyl linoleate 124-10-7, Methyl myristate 6217-54-5 7149-10-2, Vanillylamine hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **antitumor** vanillyl fatty acid amides)

10/634,641

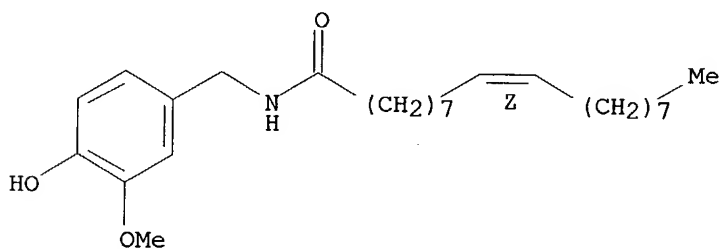
- IT 1196-92-5P, Vanillylamine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); PACT (Reactant or reagent)
(preparation of **antitumor** vanillyl fatty acid amides)
- IT 16729-47-8P, N-Vanillyllinoleamide 58493-49-5P,
N-Vanillylloleamide 104899-01-6P 457643-60-6P,
N-Vanillylricinoleamide 571203-58-2P, Dohevanil
698373-40-9P 698373-42-1P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **antitumor** vanillyl fatty acid amides)
- RN 16729-47-8 HCAPLUS
- CN 9,12-Octadecadienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



- RN 58493-49-5 HCAPLUS
- CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

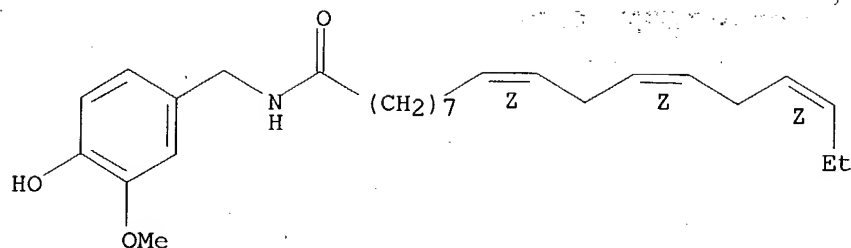


- RN 104899-01-6 HCAPLUS
- CN 9,12,15-Octadecatrienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z,12Z,15Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

DELACROIX

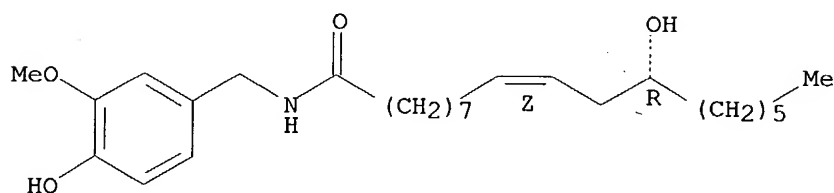
10/634,641



RN 457643-60-6 HCAPLUS

CN 9-Octadecenamide, 12-hydroxy-N-[(4-hydroxy-3-methoxyphenyl)methyl]-,
(9Z,12R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

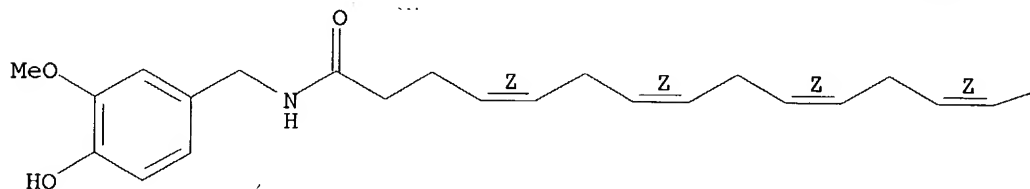


RN 571203-58-2 HCAPLUS

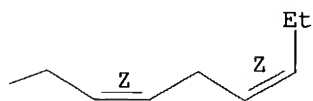
CN 4,7,10,13,16,19-Docosahexaenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-,
(4Z,7Z,10Z,13Z,16Z,19Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



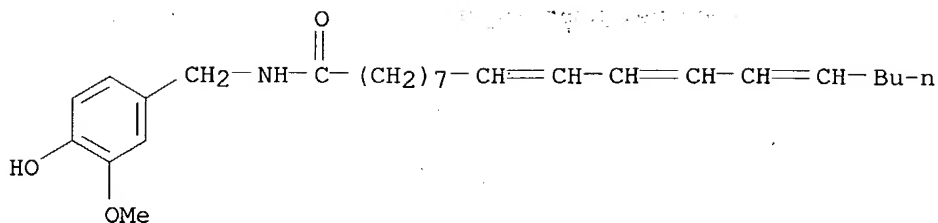
PAGE 1-B



RN 698373-40-9 HCAPLUS

CN 9,11,13-Octadecatrienamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]- (9CI)
(CA INDEX NAME)

DELACROIX

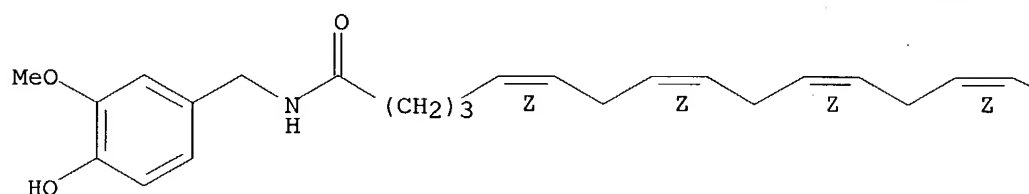


RN 698373-42-1 HCAPLUS

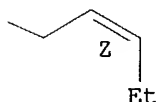
CN 5,8,11,14,17-Eicosapentaenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-,
(5Z,8Z,11Z,14Z,17Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L6 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Indirect evidence for the existence of a specific protein-mediated process for the cellular uptake of endocannabinoids has been reported, but recent results suggested that such a process, at least for AEA [N-arachidonylethanolamine (anandamide)], is facilitated uniquely by its intracellular hydrolysis by FAAH (fatty acid amide hydrolase) [Glaser, Abumrad, Fatade, Kaczocha, Studholme and Deutsch (2003) Proc. Natl. Acad. Sci. U.S.A. 100, 4269-4274]. In the present study, we show that FAAH alone cannot account for the facilitated diffusion of AEA across the cell membrane. In particular, (i) using a short incubation time (90 s) to avoid AEA hydrolysis by FAAH, AEA accumulation into rat basophilic leukemia or C6 cells was saturable at low μM concns. of substrate and non-saturable at higher concns.; (ii) time-dependent and, at low μM concns. of substrate, saturable AEA accumulation was observed also using mouse brain synaptosomes; (iii) using synaptosomes prepared from FAAH-deficient mice, saturable AEA accumulation was still observed, although with a lower efficacy; (iv) when 36 AEA and N-oleoylethanolamine analogs, most of which with Ph rings in the polar head group region, were tested as inhibitors of AEA cellular uptake, strict structural and stereochem. requirements were needed to observe significant inhibition, and in no case

the inhibition of FAAH overlapped with the inhibition of AEA uptake; and (v) AEA biosynthesis by cells and sensory neurons was followed by AEA release, and this latter process, which cannot be facilitated by FAAH, was still blocked by an inhibitor of AEA uptake. We suggest that at least one protein different from FAAH is required to facilitate AEA transport across the plasma membrane in a selective and bi-directional way.

2004:468924 Document Number 141:68639 Further evidence for the existence of a specific process for the membrane transport of anandamide. Ligresti, Alessia; Morera, Enrico; Van Der Stelt, Mario; Monory, Krisztina; Lutz, Beat; Ortar, Giorgio; Di Marzo, Vincenzo (Endocannabinoid Research Group, Institute of Biomolecular Chemistry, National Research Council, Pozzuoli, 80078, Italy). Biochemical Journal, 380(1), 265-272 (English) 2004. CODEN: BIJOAK. ISSN: 0264-6021. Publisher: Portland Press Ltd..

AB . . . particular, (i) using a short incubation time (90 s) to avoid AEA hydrolysis by FAAH, AEA accumulation into rat basophilic leukemia or C6 cells was saturable at low μM concns. of substrate and non-saturable at higher concns.; (ii) time-dependent and, atomic . . .

IT 58493-49-5 108455-80-7 128007-31-8 135391-28-5
203849-07-4 203849-08-5 223593-61-1 616884-62-9 616884-63-0
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709671-95-4 709671-98-7 709672-09-3 709672-12-8 709672-16-2
709672-19-5 709672-22-0 709672-24-2 709672-25-3 709672-26-4
709672-27-5 709672-28-6 709672-29-7 709672-30-0 709672-31-1
709672-32-2 709672-33-3

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(AEA analog, uptake; evidence for existence of specific fatty acid amide hydrolase-independent process for membrane transport of endocannabinoid anandamide (AEA))

IT 58493-49-5 128007-31-8

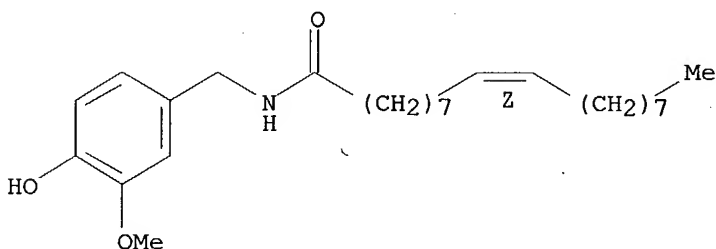
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(AEA analog, uptake; evidence for existence of specific fatty acid amide hydrolase-independent process for membrane transport of endocannabinoid anandamide (AEA))

RN 58493-49-5 HCAPLUS

CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



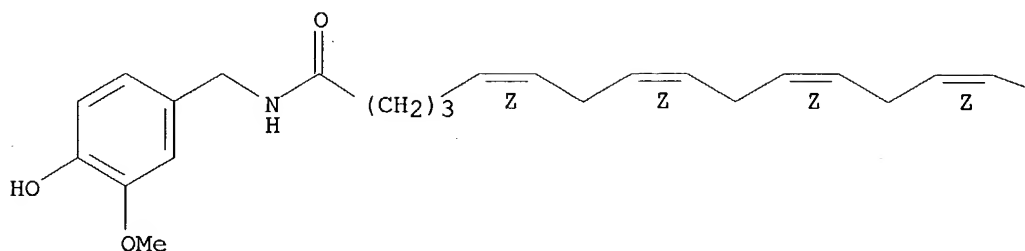
RN 128007-31-8 HCAPLUS

CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

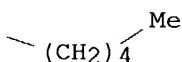
DELACROIX

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



- L6 ANSWER 4 OF 17 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
- AB On the basis of temperature dependency, saturability, selective inhibition, and substrate specificity, it has been proposed that an anandamide transporter exists. However, all of these studies have examined anandamide accumulation at long time points when downstream effects such as metabolism and intracellular sequestration are operative. In the current study, we have investigated the initial rates (<1 min) of anandamide accumulation in neuroblastoma and astrocytoma cells in culture and have determined that uptake is not saturable with increasing concentrations of anandamide. However, anandamide hydrolysis, after uptake in neuroblastoma cells, was saturable at steady-state time points (5 min), suggesting that fatty acid amide hydrolase (FAAH) may be responsible for observed saturation of uptake at long time points. In general, arvanil, olvanil, and N-(4-hydroxyphenyl)arachidonamide (AM404) have been characterized as transport inhibitors in studies using long incubations. However, we found these "transport inhibitors" did not inhibit anandamide uptake in neuroblastoma and astrocytoma cells at short time points (40 sec or less). Furthermore, we confirmed that these inhibitors in vitro were actually inhibitors of FAAH. Therefore, the likely mechanism by which the transport inhibitors raise anandamide levels to exert pharmacological effects is by inhibiting FAAH, and they should be reevaluated in this context. Immunofluorescence has indicated that FAAH staining resides mainly on intracellular membranes of neuroblastoma cells, and this finding is consistent with our observed kinetics of anandamide hydrolysis. In summary, these data suggest that anandamide uptake is a process of simple diffusion. This process is driven by metabolism and other downstream events, rather than by a specific membrane-associated anandamide carrier.
- 2003:252331 Document Number: PREV200300252331. Evidence against the presence of an anandamide transporter. Glaser, Sherrye T.; Abumrad, Nada A.; Fatade, Folayan; Kaczocha, Martin; Studholme, Keith M.; Deutsch, Dale G. [Reprint Author]. Department of Biochemistry and Cell Biology, Stony Brook

University, Stony Brook, NY, 11794, USA. ddeutsch@notes.cc.sunysb.edu.
 Proceedings of the National Academy of Sciences of the United States of
 America, (April 1 2003) Volume 100, Number 7, pp. 4269-4274. print.
 ISSN: 0027-8424 (ISSN print). Language: English.

IT . . . Concepts

Biochemistry and Molecular Biophysics; Membranes (Cell Biology)

IT Parts, Structures, & Systems of Organisms

cell; membrane

IT Diseases

astrocytoma: **neoplastic** disease, nervous system disease

Astrocytoma (MeSH)

IT Diseases

neuroblastoma: **neoplastic** disease, nervous system disease

Neuroblastoma (MeSH)

IT Chemicals & Biochemicals

AM404: enzyme inhibitor-drug; anandamide; anandamide transporter;

arvanil: enzyme inhibitor-drug; fatty acid. . .

RN 183718-77-6 (AM404)

94421-68-8 (anandamide)

128007-31-8 (arvanil)

153301-19-0 (fatty acid amide hydrolase)

58493-49-5 (olvanil)

L6 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

AB 1 Arvanil (N-arachidonoylvannillamine), a nonpungent capsaicin-anandamide
 hybrid mol., has been shown to exert biol. activities through
 VR1/CB1-dependent and -independent pathways. The authors have found that
 arvanil induces dose-dependent apoptosis in the lymphoid Jurkat T-cell
 line, but not in peripheral blood T lymphocytes. Apoptosis was assessed
 by DNA fragmentation through cell cycle and TUNEL analyses. 2
 Arvanil-induced apoptosis was initiated independently of any specific
 phase of the cell cycle, and it was inhibited by specific caspase-8 and -3
 inhibitors and by the activation of protein kinase C. In addition, kinetic
 anal. by Western blots and fluorometry showed that arvanil rapidly
 activates caspase-8, -7 and -3, and induces PARP cleavage. 3 The
 arvanil-mediated apoptotic response was greatly inhibited in the
 Jurkat-FADDDN cell line, which constitutively expresses a neg. dominant
 form of the adapter mol. Fas-associated death domain (FADD). This cell line
 does not undergo apoptosis in response to Fas (CD95) stimulation. 4 Using
 a cytofluorimetric approach, the authors have found that arvanil induced
 the production of reactive oxygen species (ROS) in both Jurkat-FADD+ and
 Jurkat-FADDDN cell lines. However, ROS accumulation only plays a residual
 role in arvanil-induced apoptosis. 5 These results demonstrate that
 arvanil-induced apoptosis is essentially mediated through a mechanism that
 is typical of type II cells, and implicates the death-inducing signaling
 complex and the activation of caspase-8. This arvanil-apoptotic activity
 is TRPV1 and CB-independent, and can be of importance for the development
 of potential anti-inflammatory and **antitumoral** drugs.

2003:955404 Document Number 140:104702 The CB1/VR1 agonist arvanil induces
 apoptosis through an FADD/caspase-8-dependent pathway. Sancho, Rocio; de
 la Vega, Laureano; Appendino, Giovanni; Di Marzo, Vincenzo; Macho,
 Antonio; Munoz, Eduardo. (Departamento de Biología Celular, Fisiología e
 Inmunología, Universidad de Córdoba, Facultad de Medicina, Córdoba, 14004,
 Spain). British Journal of Pharmacology, 140(6), 1035-1044 (English)
2003. CODEN: BJPCBM. ISSN: 0007-1188. Publisher: Nature Publishing
 Group.

AB . . . caspase-8. This arvanil-apoptotic activity is TRPV1 and

CB-independent, and can be of importance for the development of potential anti-inflammatory and antitumoral drugs.

IT **Antitumor** agents

Apoptosis

Human

Leukemia

Signal transduction, biological

(CB1/VR1 agonist arvanil induces apoptosis through an

FADD/caspase-dependent pathway)

IT **128007-31-8, Arvanil**

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)

(CB1/VR1 agonist arvanil induces apoptosis through an

FADD/caspase-dependent pathway)

IT **128007-31-8, Arvanil**

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU

(Therapeutic use); BIOL (Biological study); USES (Uses)

(CB1/VR1 agonist arvanil induces apoptosis through an

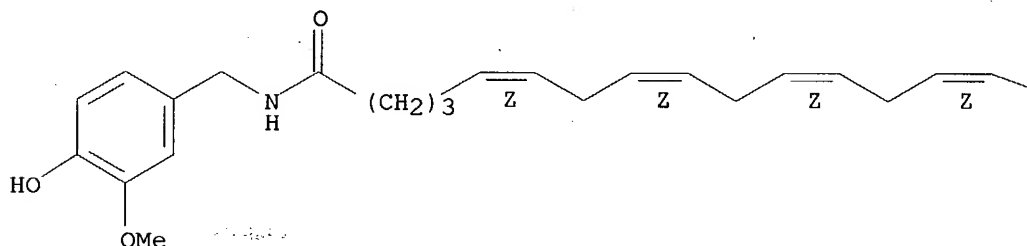
FADD/caspase-dependent pathway)

RN 128007-31-8 HCAPLUS

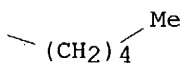
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-,
(5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L6 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Arvanil, a structural "hybrid" between the endogenous cannabinoid CB1 receptor ligand anandamide and capsaicin, is a potent agonist for the capsaicin receptor VR1 (vanilloid receptor type 1), inhibits the anandamide membrane transporter (AMT), and induces cannabimimetic responses in mice. Novel arvanil derivs. prepared by N-methylation, replacement of the amide with urea and thiourea moieties, and manipulation of the vanillyl group were evaluated for their ability to bind/activate CB1 receptors, activate VR1 receptors, inhibit the AMT and fatty acid amide hydrolase (FAAH), and produce cannabimimetic effects in mice. The

compds. did not stimulate the CB1 receptor... Methylation of the amide group decreased the activity at VR1, AMT, and FAAH. On the aromatic ring, the substitution of the 3-methoxy group with a chlorine atom or the lack of the 4-hydroxy group decreased the activity on VR1 and AMT, but not the affinity for CB1 receptors, and increased the capability to inhibit FAAH. The urea or thiourea analogs retained activity at VR1 and AMT but exhibited little affinity for CB1 receptors. The urea analog was a potent FAAH inhibitor ($IC_{50} = 2.0 \mu M$). A water-soluble analog of arvanil, O-2142, was as active on VR1, much less active on AMT and CB1, and more potent on FAAH. All compds. induced a response in the mouse "tetrad", particularly those with $EC_{50} < 10 \text{ nM}$ on VR1. However, the most potent compound, N-N'-di-(3-chloro-4-hydroxy)benzyl-arachidonamide (O-2093, ED_{50} .apprx.0.04 mg/kg), did not activate VR1 or CB1 receptors. Our findings suggest that VR1 and/or as yet uncharacterized receptors produce cannabimimetic responses in mice in vivo.

2002:203609 Document Number 137:56979 A structure/activity relationship study on arvanil, an endocannabinoid and vanilloid hybrid. Di Marzo, Vincenzo; Griffin, Graeme; De Petrocellis, Luciano; Brandi, Ines; Bisogno, Tiziana; Williams, William; Grier, Mark C.; Kulasegram, Sanjitha; Mahadevan, Anu; Razdan, Raj K.; Martin, Billy R. (Endocannabinoid Research Group, Istituto di Chimica Biomolecolare, Naples, Italy). Journal of Pharmacology and Experimental Therapeutics, 300(3), 984-991 (English) 2002. CODEN: JPETAB. ISSN: 0022-3565. OTHER SOURCES: CASREACT 137:56979. Publisher: American Society for Pharmacology and Experimental Therapeutics.

IT Amide group

Anti-inflammatory agents

Antitumor agents

Drug design

Hydroxyl group

Methoxy group

(structure/activity relationship study on arvanil)

IT 322399-59-7P, O-1861 439079-98-8P, O 1988 439079-99-9P, O 1986
439080-00-9P, O 2094 439080-01-0P, O 2093 439080-02-1P, O 1987
439080-03-2P 439080-04-3P, O 2109 439080-05-4P, O 2142

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(structure/activity relationship study on arvanil)

IT 128007-31-8P, Arvanil

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(structure/activity relationship study on arvanil)

IT 322399-59-7P, O-1861

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

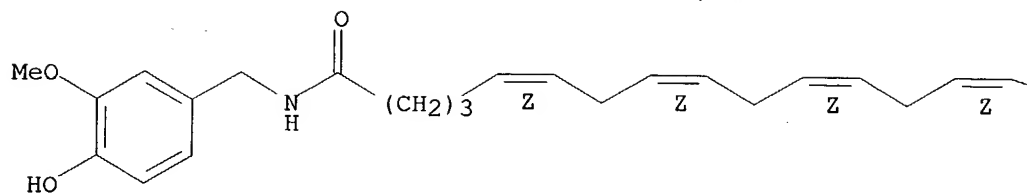
(structure/activity relationship study on arvanil)

RN 322399-59-7 HCAPLUS

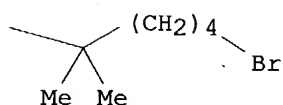
CN 5,8,11,14-Eicosatetraenamide, 20-bromo-N-[(4-hydroxy-3-methoxyphenyl)methyl]-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



IT 128007-31-8P, Arvanil

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

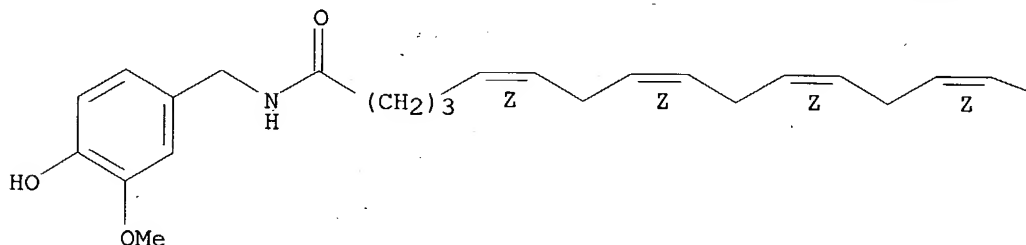
(structure/activity relationship study on arvanil)

RN 128007-31-8 HCAPLUS

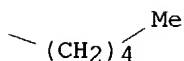
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L6 ANSWER 7 OF 17 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

AB New uses warranted for cannabinoids? Recent data indicate that synthetic

DELACROIX

- or endogenous substances activating the receptor for marijuana's psychotropic component might be used as templates for the development of new anti-**cancer** drugs.
- 2002213774 EMBASE Targeting the endocannabinoid system in **cancer** therapy: A call for further research. Bifulco M.; Di Marzo V.. M. Bifulco, Dipto. di Scienze Farmaceutiche, Universita di Salerno, Fisciano, Salerno, Italy. maubiful@unina.it. Nature Medicine 8/6 (547-550) 2002. Refs: 30. ISSN: 1078-8956. CODEN: NAMEFI. Pub. Country: United States. Language: English. Summary Language: English.
- TI Targeting the endocannabinoid system in **cancer** therapy: A call for further research.
- AB . . . or endogenous substances activating the receptor for marijuana's psychotropic component might be used as templates for the development of new anti-**cancer** drugs.
- CT Medical Descriptors:
- ***cancer therapy**
 - ***cancer research**
 - drug targeting
 - drug mechanism
 - antineoplastic activity
 - nausea: DT, drug therapy
 - vomiting: DT, drug therapy
 - tumor growth
 - cancer inhibition**
 - drug dependence
 - drug tolerance
 - human
 - nonhuman
 - review
 - priority journal
 - *cannabinoid receptor
 - *cannabinoid receptor affecting agent: DV, drug development
 - *cannabinoid receptor affecting agent: PD, pharmacology
 - *cannabinoid receptor affecting agent: . . .
- RN (anandamide) 94421-68-8; (arvanil) **128007-31-8**; (tetrahydrocannabinol) 1972-08-3; (dronabinol) 7663-50-5; (nabilone) 51022-71-0; (cannabis) 8001-45-4, 8063-14-7
- L6 ANSWER 8 OF 17 MEDLINE on STN DUPLICATE 2
- AB Palmitoylethanolamide (PEA) is a bioactive fatty acid amide belonging to the class of N-acyl-ethanolamines (NAEs). This compound has been known since the 1950s for its anti-inflammatory effects, but was re-discovered only after the finding that another NAE, arachidonoyl-ethanolamide (anandamide, AEA), could act as an endogenous ligand of cannabinoid receptors. Although a similar function for PEA has also been proposed, this compound does not activate the two cannabinoid receptor subtypes described to date. PEA and AEA are co-synthesized by cells, and PEA might act as an 'entourage' compound for AEA, i.e. as an endogenous enhancer of AEA biological actions. Indeed, long-term treatment of human breast **cancer** cells (HBCCs) with PEA downregulates the expression of the enzyme responsible for AEA degradation, the fatty acid amide hydrolase, thereby leading to an enhancement of AEA-induced, and cannabinoid CB1 receptor-mediated, cytostatic effect on HBCCs. AEA is also a full agonist for the receptors of another class of bioactive fatty acid amides, the N-acyl-vanillyl-amines (e.g. capsaicin and olvanil). These sites of action are known as vanilloid receptors of type 1 (VR1). PEA enhances the

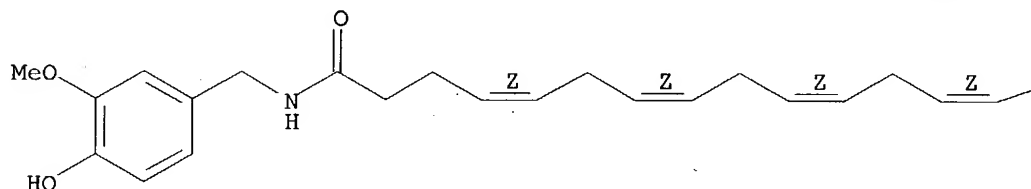
VR1-mediated effects of AEA and capsaicin on calcium influx into cells. These 'entourage' effects of PEA might be attributable to modulation of VR1 activity, and could underlie the enhancement by PEA, described here for the first time, of the antiproliferative effects of VR1 receptor agonists.

2003059673. PubMed ID: 12570018. Effect on **cancer** cell proliferation of palmitoylethanolamide, a fatty acid amide interacting with both the cannabinoid and vanilloid signalling systems. De Petrocellis Luciano; Bisogno Tiziana; Ligresti Alessia; Bifulco Maurizio; Melck Dominique; Di Marzo Vincenzo. (Istituto di Cibernetica Eduardo Caianiello, Consiglio Nazionale delle Ricerche, Comprensorio Olivetti, Pozzuoli, Napoli, Italy.) Fundamental & clinical pharmacology, (2002 Aug) 16 (4) 297-302. Journal code: 8710411. ISSN: 0767-3981. Pub. country: England: United Kingdom. Language: English.
- TI Effect on **cancer** cell proliferation of palmitoylethanolamide, a fatty acid amide interacting with both the cannabinoid and vanilloid signalling systems.
- AB . . . an 'entourage' compound for AEA, i.e. as an endogenous enhancer of AEA biological actions. Indeed, long-term treatment of human breast **cancer** cells (HBCCs) with PEA downregulates the expression of the enzyme responsible for AEA degradation, the fatty acid amide hydrolase, thereby. . . .
- CT Check Tags: Female; Human; Support, Non-U.S. Gov't
Anti-Inflammatory Agents, Non-Steroidal: PD, pharmacology
*Antineoplastic Agents: PD, pharmacology
Breast Neoplasms
*Cannabinoids: ME, metabolism
*Capsaicin: AA, analogs & derivatives
Capsaicin: PD, pharmacology
Cell Division: DE, drug effects
Dose-Response Relationship, . . .
- RN 404-86-4 (Capsaicin); 544-31-0 (palmidrol); **58493-49-5 (olvanil)**
- L6 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
- AB There are few effective clin. studies to inhibit the growth of multidrug resistance tumor cells. We have been interested in the physiol. actions of capsaicin (CAP), the pungent ingredient in hot chilli peppers, and polyunsatd. fatty acids, for example docosahexaenoic acid (DHA), extracted from fish oil. In this study, we synthesized a new vanillylamide derivative, N-docosahexaenoylvanillylamide (dohevanil), to investigate the inhibitory effect of dohevanil on growth of HeLa cells and taxol-tolerant HeLa cells. As a result, dohevanil has more potent inhibitory effect than CAP for both taxol-sensitive HeLa cells and taxol-tolerant HeLa cells. Particularly, the simultaneous addition of dohevanil and taxol more strongly induced cell death of taxol-tolerant HeLa cells. There results obtained in this study suggest that dohevanil has stronger inhibitory effect than CAP for the multidrug resistance cells.
- 2004:272650 Document Number 141:99178 Effect of capsaicin and N-docosahexaenoyl-vanillylamide on growth of taxol-tolerant HeLa cells. Jin, Yongfu; Ishihata, Kimie; Kajiyama, Shin-ichiro; Fukusaki, Ei-ichiro; Kobayashi, Akio; Baba, Naomichi; Tada, Mikiro; Takahata, Kyoya (Graduate School of Natural Science and Technology, Okayama University, Japan). Nippon Shokuhin Kagaku Gakkaishi, 9(2), 50-53 (Japanese) 2002. CODEN: NSKGF4. ISSN: 1341-2094. Publisher: Nippon Shokuhin Kagaku Gakkai.
- IT **Antitumor** agents
Human
Multidrug resistance

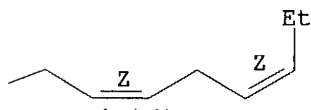
- (effect of capsaicin and N-docosahexaenoyl-vanillylamide on growth of taxol-tolerant HeLa cells)
- IT 404-86-4, Capsaicin 33069-62-4, Taxol 571203-58-2, Dohevanil
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (effect of capsaicin and N-docosahexaenoyl-vanillylamide on growth of taxol-tolerant HeLa cells)
- IT 571203-58-2, Dohevanil
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (effect of capsaicin and N-docosahexaenoyl-vanillylamide on growth of taxol-tolerant HeLa cells)
- RN 571203-58-2 HCAPLUS
- CN 4,7,10,13,16,19-Docosahexaenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (4Z,7Z,10Z,13Z,16Z,19Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



- L6 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
- AB A review. Induction of **cancer** cell apoptosis by docosahexaenoic acid (DHA) derivative Dohevanil of a spicy component capsaicin is reviewed including the structure of capsaicin and its receptor, **antitumor** effects of capsaicin as well as **antitumor** effects of Dohevanil.
 2002:937871 Document Number 139:142982 Induction of **cancer** cell apoptosis by docosahexaenoic acid (DHA) derivative Dohevanil of a spicy component capsaicin. Takahata, Kyoya; Ishihata, Kimie; Kim, Eifuku (Department of Agriculture, Okayama University, Japan). New Food Industry, 44(10), 6-12 (Japanese) 2002. CODEN: NYFIAM. ISSN: 0547-0277. Publisher: Shokuhin Shizai Kenkyukai.
- TI Induction of **cancer** cell apoptosis by docosahexaenoic acid (DHA) derivative Dohevanil of a spicy component capsaicin
- AB A review. Induction of **cancer** cell apoptosis by docosahexaenoic acid (DHA) derivative Dohevanil of a spicy component capsaicin is reviewed including the structure of capsaicin and its receptor, **antitumor** effects of capsaicin as well as **antitumor** effects of Dohevanil.
- ST review **antitumor** apoptosis docosahexaenoic acid deriv Dohevanil capsaicin
- IT **Antitumor** agents

Apoptosis

(induction of **cancer** cell apoptosis by DHA derivative Dohevanil, a spicy component capsaicin)

IT Capsaicin receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induction of **cancer** cell apoptosis by DHA derivative Dohevanil, a spicy component capsaicin)

IT 404-86-4, Capsaicin 6217-54-5, Docosaehxaenoic acid 571203-58-2, Dohevanil

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of **cancer** cell apoptosis by DHA derivative Dohevanil, a spicy component capsaicin)

IT 571203-58-2, Dohevanil

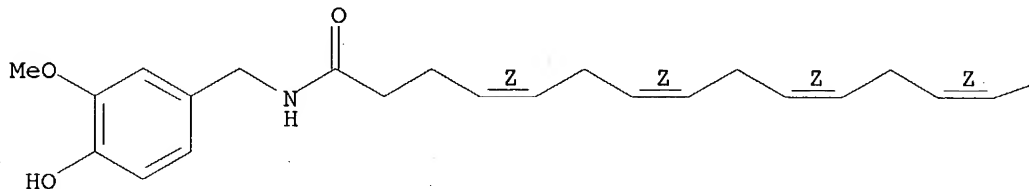
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of **cancer** cell apoptosis by DHA derivative Dohevanil, a spicy component capsaicin)

RN 571203-58-2 HCAPLUS

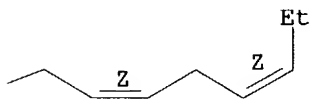
CN 4,7,10,13,16,19-Docosaehxaenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (4Z,7Z,10Z,13Z,16Z,19Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



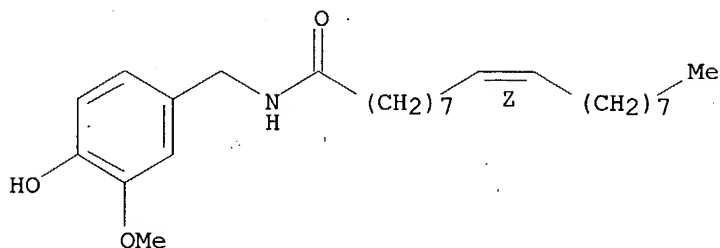
L6 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

AB The endogenous cannabinoid receptor agonist anandamide (AEA) and the related compound palmitoylethanolamide (PEA) are inactivated by transport into cells followed by metabolism by fatty acid amide hydrolase (FAAH). The cellular uptake of AEA has been characterized in detail, whereas less is known about the properties of the PEA uptake, in particular in neuronal cells. In the present study, the pharmacol. and functional properties of PEA and AEA uptake have been investigated in mouse Neuro-2a neuroblastoma and, for comparison, in rat RBL-2H3 basophilic leukemia cells. Saturable uptake of PEA and AEA into both cell lines were demonstrated with apparent KM values of 28 μ M (PEA) and 10 μ M (AEA) in Neuro-2a cells, and 30 μ M (PEA) and 9.3 μ M (AEA) in RBL-2H3 cells. Both PEA and AEA uptake showed temperature-dependence but only the AEA uptake was sensitive to treatment with Pronase and phenylmethylsulfonyl fluoride.

The AEA uptake was inhibited by AM404, 2-arachidonoylglycerol (2-AG), R1- and S1-methanandamide, arachidonic acid and olvanil with similar potencies for the two cell types. PEA, up to a concentration of 100 μ M, did not affect AEA uptake in either cell line. AEA, 2-AG, arachidonic acid, R1-methanandamide, Δ 9-THC, and cannabidiol inhibited PEA transport in both cell lines. The non-steroidal anti-inflammatory drug indomethacin inhibited the AEA uptake but had very weak effects on the uptake of PEA. From these data, it can be concluded that PEA is transported in to cells both by passive diffusion and by a facilitated transport that is pharmacol. distinguishable from AEA uptake.

- 2001:322837 Document Number 135:132395 Characterization of palmitoylethanolamide transport in mouse Neuro-2a neuroblastoma and rat RBL-2H3 basophilic leukaemia cells: comparison with anandamide. Jacobsson, Stig O. P.; Fowler, Christopher J. (Department of Pharmacology and Clinical Neuroscience, Department of Odontology, Umea University, Umea, SE-901 87, Swed.). British Journal of Pharmacology, 132(8), 1743-1754 (English) 2001. CODEN: BJPCBM. ISSN: 0007-1188. Publisher: Nature Publishing Group.
- AB . . . properties of PEA and AEA uptake have been investigated in mouse Neuro-2a neuroblastoma and, for comparison, in rat RBL-2H3 basophilic **leukemia** cells. Saturable uptake of PEA and AEA into both cell lines were demonstrated with apparent KM values of 28 μ M. . .
- IT 53-86-1, Indomethacin 329-98-6, Phenylmethylsulfonyl fluoride 506-32-1, Arachidonic acid 1972-08-3, Δ 9-THC 9036-06-0, Pronase 13956-29-1, Cannabidiol 15687-27-1, Ibuprofen 53847-30-6, **58493-49-5**, Olvanil 157182-49-5, R-Methanandamide 157182-50-8, S-Methanandamide
- RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of palmitoylethanolamide transport in neuronal cells)
- IT **58493-49-5**, Olvanil
- RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of palmitoylethanolamide transport in neuronal cells)
- RN 58493-49-5 HCAPLUS
- CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



- L6 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
- AB The effects of the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) upon rat C6 glioma cell proliferation were

examined and compared with a series of synthetic cannabinoids and related compds. Cells were treated with the compds. each day and cell proliferation was monitored for up to 5 days of exposure. AEA time- and concentration-dependently inhibited C6 cell proliferation. After 4 days of treatment, AEA and 2-AG inhibited C6 cell proliferation with similar potencies (IC50 values of 1.6 and 1.8 μ M, resp.), whereas palmitoylethanolamide showed no significant antiproliferative effects at concns. up to 10 μ M. The antiproliferative effects of both AEA and 2-AG were blocked completely by a combination of antagonists at cannabinoid receptors (SR141716A and SR144528 or AM251 and AM630) and vanilloid receptors (capsazepine) as well as by α -tocopherol (0.1 and 10 μ M), and reduced by calpeptin (10 μ M) and fumonisins B1 (10 μ M), but not by L-cycloserine (1 and 100 μ M). CP 55,940, JWH015, olvanil, and arachidonoyl-serotonin were all found to affect C6 glioma cell proliferation (IC50 values of 5.6, 3.2, 5.5, and 1.6 μ M, resp.), but the inhibition could not be blocked by cannabinoid + vanilloid receptor antagonists. It is concluded that the antiproliferative effects of the endocannabinoids upon C6 cells are brought about by a mechanism involving combined activation of both vanilloid receptors and to a lesser extent cannabinoid receptors, and leading to oxidative stress and calpain activation. However, there is at present no obvious universal mechanism whereby plant-derived, synthetic, and endogenous cannabinoids affect cell viability and proliferation.

2001:884754 Document Number 136:161001 Inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids. Relative involvement of cannabinoid and vanilloid receptors. Jacobsson, Stig O. P.; Wallin, Thomas; Fowler, Christopher J. (Departments of Pharmacology and Clinical Neuroscience and Odontology, Umea University, Umea, Swed.). Journal of Pharmacology and Experimental Therapeutics, 299(3), 951-959 (English) 2001. CODEN: JPETAB. ISSN: 0022-3565. Publisher: American Society for Pharmacology and Experimental Therapeutics.

IT **Antitumor** agents

(glioma; mechanism of the inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids)

IT 404-86-4, Capsaicin 544-31-0, Palmitoylethanolamide 53847-30-6
58493-49-5, Olvanil 83002-04-4, CP55940 94421-68-8, Anandamide
 131513-18-3, WIN55212 155471-08-2, JWH015 157182-49-5 187947-37-1
 RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action);
 PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological
 study); USES (Uses)

(mechanism of the inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids)

IT **58493-49-5**, Olvanil

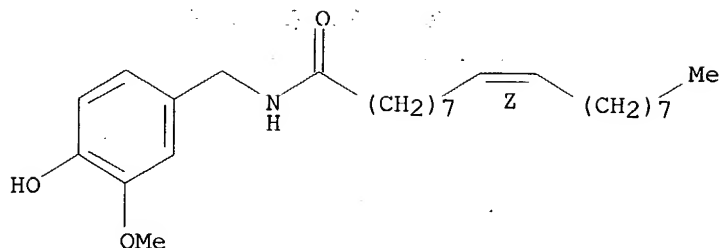
RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action);
 PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological
 study); USES (Uses)

(mechanism of the inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids)

RN 58493-49-5 HCAPLUS

CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA
 INDEX NAME)

Double bond geometry as shown.



- L6 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN
- AB Pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating the peripheral receptor CB1 of cannabinoids (Markush structures) are disclosed. N-(4-hydroxy-3-methoxybenzyl)oleylamide (I) was prepared by the reaction of oleic acid, 4-methylmorpholine, and 4-hydroxy-3-methoxybenzylamine hydrochloride. The specific binding of I to mouse neuroblastoma cells and rat **leukemia** basophil cell was 1.64 μM and >15 μM , resp. A tablet contained 30, lactose 85, corn starch 75, talc 6, magnesium stearate 2, and CM-cellulose 2 mg.
- 2000:209882 Document Number 132:241970 Pharmaceutical compositions containing N-acylvanillinamide derivatives capable of activating peripheral cannabinoid receptors. Bisogno, Tiziana; Della Valle, Francesco; De Petrocellis, Luciano; Di Marzo, Vincenzo; Marcolongo, Gabriele; Melck, Dominique (Innovet Italia S.r.l., Italy; Consiglio Nazionale Delle Ricerche). PCT Int. Appl. WO 2000016756 A2 20000330, 68 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-EP6980 19990921. PRIORITY: IT 1998-MI2064 19980924.
- AB . . . the reaction of oleic acid, 4-methylmorpholine, and 4-hydroxy-3-methoxybenzylamine hydrochloride. The specific binding of I to mouse neuroblastoma cells and rat **leukemia** basophil cell was 1.64 μM and >15 μM , resp. A tablet contained 30, lactose 85, corn starch 75, talc 6, . . .
- IT **Antitumor** agents
(mammary gland carcinoma; pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating peripheral cannabinoid receptors)
- IT **Antitumor** agents
(mammary gland; pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating peripheral cannabinoid receptors)
- IT Mammary gland
Mammary gland
Prostate gland
Prostate gland
(**neoplasm**, inhibitors; pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating peripheral cannabinoid receptors)
- IT **Antitumor** agents
Mouthwashes
(pharmaceutical compns. containing N-acylvanillinamide derivs. capable of

activating peripheral cannabinoid receptors)

IT **Antitumor** agents
(prostate carcinoma; pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating peripheral cannabinoid receptors)

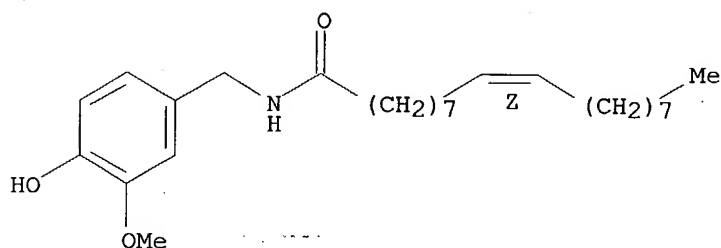
IT **Antitumor** agents
(prostate gland; pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating peripheral cannabinoid receptors)

IT **58493-49-5P 69693-13-6P 128007-31-8P**
261946-50-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating peripheral cannabinoid receptors)

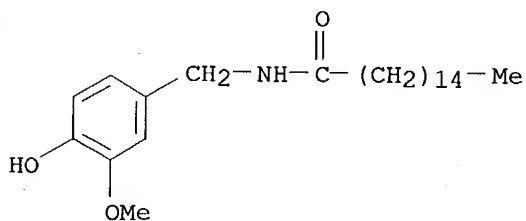
IT **58493-49-5P 69693-13-6P 128007-31-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. containing N-acylvanillinamide derivs. capable of activating peripheral cannabinoid receptors)

RN 58493-49-5 HCAPLUS
CN 9-Octadecenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

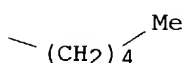
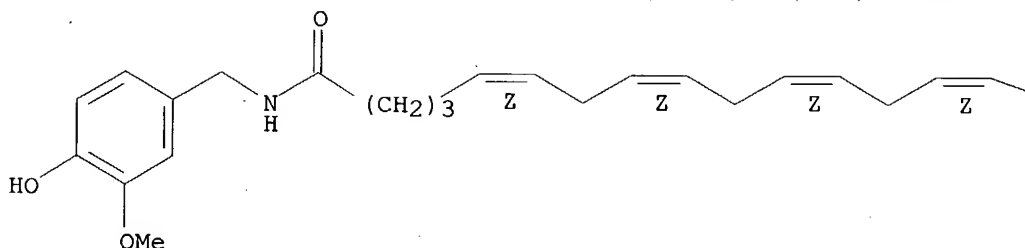


RN 69693-13-6 HCAPLUS
CN Hexadecanamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)



RN 128007-31-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L6 ANSWER 14 OF 17 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

AB The long history of the medicinal use of Cannabis sativa and, more recently, of its chemical constituents, the cannabinoids, suggests that also the endogenous ligands of cannabinoid receptors, the endocannabinoids, and, particularly, their derivatives may be used as therapeutic agents. Studies aimed at correlating the tissue and body fluid levels of endogenous cannabinoid-like molecules with pathological conditions have been started and may lead to identify those diseases that can be alleviated by drugs that either mimic or antagonize the action of these substances, or modulate their biosynthesis and degradation. Hints for the therapeutic applications of endocannabinoids, however, can be obtained also from our previous knowledge of marijuana medicinal properties. In this article, we discuss the **anti-tumor** and **anti-inflammatory** activity of: (1) the endocannabinoids anandamide (arachidonylethanolamide) and 2-arachidonoyl glycerol; (2) the bioactive fatty acid amides palmitoylethanolamide and oleamide; and (3) some synthetic derivatives of these compounds, such as the N-acyl-vanillyl-amines. Furthermore, the possible role of cannabimimetic fatty acid derivatives in the pathological consequences of **cancer** and inflammation, such as cachexia, wasting syndrome, chronic pain and local vasodilation, will be examined. (C) 2000 Elsevier Science Ireland Ltd.

2000425328 EMBASE Endocannabinoids and fatty acid amides in **cancer**, inflammation and related disorders. De Petrocellis L.; Melck D.; Bisogno T.; Di Marzo V.. V. Di Marzo, Ist. Chimica Molecole Int. Biologico, C.N.R., via Toiano 6, 80072 Arco Felice, Napoli, Italy.
vdimarzo@icmib.na.cnr.it. Chemistry and Physics of Lipids 108/1-2 (191-209) 2000.

Refs: 104.

ISSN: 0009-3084. CODEN: CPLIA4.

Publisher Ident.: S 0009-3084(00)00196-1. Pub. Country: Ireland. Language: English. Summary Language: English.

TI Endocannabinoids and fatty acid amides in **cancer**, inflammation

and related disorders.

AB . . . endocannabinoids, however, can be obtained also from our previous knowledge of marijuana medicinal properties. In this article, we discuss the **anti-tumor** and **anti-inflammatory** activity of: (1) the endocannabinoids anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol; (2) the bioactive fatty acid amides palmitoylethanolamide and oleamide; and. . . these compounds, such as the N-acyl-vanillyl-amines. Furthermore, the possible role of cannabinimetic fatty acid derivatives in the pathological consequences of **cancer** and inflammation, such as cachexia, wasting syndrome, chronic pain and local vasodilation, will be examined. (C) 2000 Elsevier Science Ireland. . .

CT Medical Descriptors:

***cancer: DT, drug therapy**
 *inflammation: DT, drug therapy
 *chronic pain: CO, complication
 *chronic pain: DT, drug therapy
 *chronic pain: ET, etiology
 *wasting syndrome: CO, complication
 *wasting syndrome: . . .

RN. . . methyl 3 (morpholinomethyl) 6 (1 naphthoyl)pyrrolo[1,2,3 de][1,4]benzoxazine) 134959-51-6; (4 (1,1 dimethylheptyl) 1',2',3',4',5',6' hexahydro 2,3' dihydroxy 6' (3 hydroxypropyl)biphenyl) 83003-12-7; (olvanil) **58493-49-5**

L6 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2004 ACS on STN

AB Anandamide and 2-arachidonoylglycerol (2-AG), two endogenous ligands of the CB1 and CB2 cannabinoid receptor subtypes, inhibit the proliferation of PRL-responsive human breast **cancer** cells (HBCCs) through down-regulation of the long form of the PRL receptor (PRLr). Here the authors report that (1) anandamide and 2-AG inhibit the nerve growth factor (NGF)-induced proliferation of HBCCs through suppression of the levels of NGF Trk receptors; (2) inhibition of PRLr levels results in inhibition of the proliferation of other PRL-responsive cells, the prostate **cancer** DU-145 cell line; and (3) CB1-like cannabinoid receptors are expressed in HBCCs and DU-145 cells and mediate the inhibition of cell proliferation and Trk/PRLr expression. β -NGF-induced HBCC proliferation was potently inhibited (IC₅₀ = 50-600 nM) by the synthetic cannabinoid HU-210, 2-AG, anandamide, and its metabolically stable analogs, but not by the anandamide congener, palmitoylethanolamide, or the selective agonist of CB2 cannabinoid receptors, BML-190. The effect of anandamide was blocked by the CB1 receptor antagonist, SR141716A, but not by the CB2 receptor antagonist, SR144528. Anandamide and HU-210 exerted a strong inhibition of the levels of NGF Trk receptors as detected by Western immunoblotting; this effect was reversed by SR141716A. When induced by exogenous PRL, the proliferation of prostate DU-145 cells was potently inhibited (IC₅₀ = 100-300 nM) by anandamide, 2-AG, and HU-210. Anandamide also down-regulated the levels of PRLr in DU-145 cells. SR141716A attenuated these two effects of anandamide. HBCCs and DU-145 cells were shown to contain (1) transcripts for CB1 and, to a lesser extent, CB2 cannabinoid receptors, (2) specific binding sites for [3H]SR141716A that could be displaced by anandamide, and (3) a CB1 receptor-immunoreactive protein. These findings suggest that endogenous cannabinoids and CB1 receptor agonists are potential neg. effectors of PRL- and NGF-induced biol. responses, at least in some **cancer** cells.

2000:4740 Document Number 132:132746 Suppression of nerve growth factor Trk

- receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate **cancer** cell proliferation. Melck, Dominique; De Petrocellis, Luciano; Orlando, Pierangelo; Bisogno, Tiziana; Laezza, Chiara; Bifulco, Maurizio; Di Marzo, Vincenzo (Istituto per la Chimica di Molecole di Interesse Biologico, Consiglio Nazionale delle Ricerche, Arco Felice, 80072, Italy). *Endocrinology*, 141(1), 118-126 (English) 2000. CODEN: ENDOAO. ISSN: 0013-7227. Publisher: Endocrine Society.
- TI Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate **cancer** cell proliferation
- AB . . . 2-arachidonoylglycerol (2-AG), two endogenous ligands of the CB1 and CB2 cannabinoid receptor subtypes, inhibit the proliferation of PRL-responsive human breast **cancer** cells (HBCCs) through down-regulation of the long form of the PRL receptor (PRLr). Here the authors report that (1) anandamide. . . NGF Trk receptors; (2) inhibition of PRLr levels results in inhibition of the proliferation of other PRL-responsive cells, the prostate **cancer** DU-145 cell line; and (3) CB1-like cannabinoid receptors are expressed in HBCCs and DU-145 cells and mediate the inhibition of. . . endogenous cannabinoids and CB1 receptor agonists are potential neg. effectors of PRL- and NGF-induced biol. responses, at least in some **cancer** cells.
- ST endocannabinoid NGF prolactin receptor breast prostate **cancer** proliferation
- IT Cannabinoid receptors
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(CB1; endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate **cancer** cell proliferation)
- IT **Antitumor** agents
Proliferation inhibition
(endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate **cancer** cell proliferation)
- IT Neurotrophic factor receptors
Prolactin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate **cancer** cell proliferation)
- IT Mammary gland
Prostate gland
(**neoplasm**; endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate **cancer** cell proliferation)
- IT 53847-30-6 94421-68-8, Anandamide 112830-95-2, HU-210
128007-31-8, Arvanil 157182-49-5, (R)-Methanandamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate **cancer** cell proliferation)
- IT 9002-62-4, Prolactin, biological studies 9061-61-4, Nerve growth factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)

(endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate cancer cell proliferation)

IT 128007-31-8, Arvanil

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

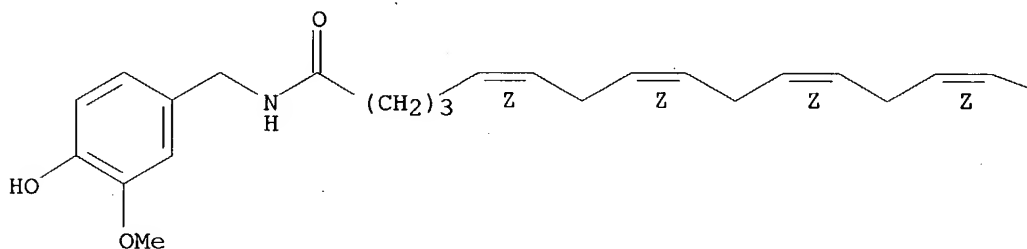
(endocannabinoids suppression of NGF Trk receptors and prolactin receptors involvement in inhibition of human breast and prostate cancer cell proliferation)

RN 128007-31-8 HCAPLUS

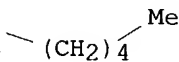
CN 5,8,11,14-Eicosatetraenamide, N-[(4-hydroxy-3-methoxyphenyl)methyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



- L6 ANSWER 16 OF 17 MEDLINE on STN DUPLICATE 4
- AB We investigated the effect of changing the length and degree of unsaturation of the fatty acyl chain of N-(3-methoxy-4-hydroxy)-benzyl-cis-9-octadecenoamide (olvanil), a ligand of vanilloid receptors, on its capability to: (i) inhibit anandamide-facilitated transport into cells and enzymatic hydrolysis, (ii) bind to CB1 and CB2 cannabinoid receptors, and (iii) activate the VR1 vanilloid receptor. Potent inhibition of [(14)C]anandamide accumulation into cells was achieved with C20:4 n-6, C18:3 n-6 and n-3, and C18:2 n-6 N-acyl-vanillyl-amides (N-AVAMs). The saturated analogues and Delta(9)-trans-olvanil were inactive. Activity in CB1 binding assays increased when increasing the number of cis-double bonds in a n-6 fatty acyl chain and, in saturated N-AVAMs, was not greatly sensitive to decreasing the chain length. The C20:4 n-6 analogue (arvanil) was a potent inhibitor of anandamide accumulation (IC(50) = 3.6 microM) and was 4-fold more potent than anandamide on CB1 receptors (Ki = 0.25-0.52 microM), whereas the C18:3 n-3 N-AVAM was more selective than arvanil for the uptake (IC(50) = 8.0 microM) vs CB1 receptors (Ki = 3.4 microM). None of the compounds efficiently inhibited [(14)C]anandamide hydrolysis or bound to CB2 receptors. All N-AVAMs activated the cation

currents coupled to VR1 receptors overexpressed in *Xenopus* oocytes. In a simple, intact cell model of both vanilloid- and anandamide-like activity, i.e., the inhibition of human breast **cancer** cell (HBCC) proliferation, arvanil was shown to behave as a "hybrid" activator of cannabinoid and vanilloid receptors.

Copyright 1999 Academic Press.

1999382278. PubMed ID: 10448105. Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors. Melck D; Bisogno T; De Petrocellis L; Chuang H; Julius D; Bifulco M; Di Marzo V. (Istituto per la Chimica di Molecole di Interesse Biologico, Universita di Napoli Federico II, 80131, Napoli, Italy.) Biochemical and biophysical research communications, (1999 Aug 19) 262 (1) 275-84. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB . . . *Xenopus* oocytes. In a simple, intact cell model of both vanilloid- and anandamide-like activity, i.e., the inhibition of human breast **cancer** cell (HBCC) proliferation, arvanil was shown to behave as a "hybrid" activator of cannabinoid and vanilloid receptors. Copyright 1999 Academic Press.

RN 404-86-4 (Capsaicin); 58493-49-5 (olvanil); 94421-68-8 (anandamide)

L6 ANSWER 17 OF 17 MEDLINE on STN

DUPLICATE 5

AB The chemical similarity between some synthetic agonists of vanilloid receptors, such as olvanil (N-vanillyl-cis-9-octadecenoamide), and the 'endocannabinoid' anandamide (arachidonoyl-ethanolamide, AEA), suggests possible interactions between the cannabinoid and vanilloid signalling systems. Here we report that olvanil is a stable and potent inhibitor of AEA facilitated transport into rat basophilic leukemia (RBL-2H3) cells. Olvanil blocked both the uptake and the hydrolysis of [¹⁴C]AEA by intact RBL-2H3 cells (IC₅₀ = 9 microM), while capsaicin and pseudocapsaicin (N-vanillyl-nonanamide) were much less active. Olvanil was more potent than previously reported inhibitors of AEA facilitated transport, i.e. phloretin (IC₅₀ = 80 microM), AM404 (12.9% inhibition at 10 microM) or oleoylethanolamide (27.5% inhibition at 10 microM). Olvanil was a poor inhibitor of [¹⁴C]AEA hydrolysis by RBL-2H3 and N18TG2 cell membranes, suggesting that the inhibitory effect on [¹⁴C]AEA breakdown observed in intact cells was due to inhibition of [¹⁴C]AEA uptake. Olvanil was stable to enzymatic hydrolysis, and (i) displaced the binding of high affinity cannabinoid receptor ligands to membrane preparations from N18TG2 cells and guinea pig forebrain (K_i = 1.64-7.08 microM), but not from cells expressing the CB2 cannabinoid receptor subtype; (ii) inhibited forskolin-induced cAMP formation in intact N18TG2 cells (IC₅₀ = 1.60 microM), this effect being reversed by the selective CB1 antagonist SR141716A. Pseudocapsaicin, but not capsaicin, also selectively bound to CB1 receptor-containing membranes. These data suggest that some of the analgesic actions of olvanil may be due to its interactions with the endogenous cannabinoid system, and may lead to the design of a novel class of cannabimimetics with potential therapeutic applications as analgesics.

1999015786. PubMed ID: 9801167. Interactions between synthetic vanilloids and the endogenous cannabinoid system. Di Marzo V; Bisogno T; Melck D; Ross R; Brockie H; Stevenson L; Pertwee R; De Petrocellis L. (Istituto per la Chimica di Molecole di Interesse Biologico, CNR, Napoli, Italy.. vdm@trinc.icmib.na.cnr.it) . FEBS letters, (1998 Oct 9) 436 (3) 449-54. Journal code: 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

10/634,641

AB . . . signalling systems. Here we report that olvanil is a stable and potent inhibitor of AEA facilitated transport into rat basophilic **leukemia** (RBL-2H3) cells. Olvanil blocked both the uptake and the hydrolysis of [14C]AEA by intact RBL-2H3 cells (IC50 = 9 microM),. . .

CT . . .
pharmacokinetics

- *Arachidonic Acids: PD, pharmacology
- *Cannabinoids: PK, pharmacokinetics
- *Capsaicin: AA, analogs & derivatives
- Capsaicin: PD, pharmacology
- Cell Line
- Endocannabinoids
- Kinetics

- Leukemia, Basophilic, Acute**
- Macrophages
- Mice
- Neuroblastoma
- Rats

- Receptors, Drug: AG, agonists
- *Receptors, Drug: PH, physiology
- Tumor Cells, Cultured

RN 404-86-4 (Capsaicin); **58493-49-5 (olvanil)**; 94421-68-8 (anandamide)